

Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER P32185
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) <b>09/831652</b>
INTERNATIONAL APPLICATION NO. PCT/US99/26746	INTERNATIONAL FILING DATE 12 November 1999	PRIORITY DATE CLAIMED 12 November 1998
TITLE OF INVENTION <b>NOVEL METHOD OF TREATMENT</b>		
APPLICANT(S) FOR DO/EO/US <b>Lisa BENINCOSA and William JUSKO</b>		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1.  This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2.  This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3.  This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4.  A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5.  A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a.  is transmitted herewith (required only if not transmitted by the International Bureau).
  - b.  has been transmitted by the International Bureau.
  - c.  is not required, as the application was filed in the United States Receiving Office (RO/US).
6.  A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7.  Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a.  are transmitted herewith (required only if not transmitted by the International Bureau).
  - b.  have been transmitted by the International Bureau.
  - c.  have not been made; however, the time limit for making such amendments has NOT expired.
  - d.  have not been made and will not be made.
8.  A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9.  An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10.  A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern other document(s) or information included:**

11.  An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.
12.  An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13.  A **FIRST** preliminary amendment.
14.  A **SECOND** or **SUBSEQUENT** preliminary amendment.
15.  Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/US99/26746, filed 12 November 1999.
16.  A substitute specification.
17.  A change of power of attorney and/or address letter.
18.  An Abstract on a separate sheet of paper.
19.  Other items or information:

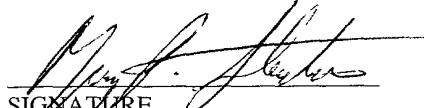
US APPLICATION NO/ (if known see 37 CFR 1.50) <b>09/831652</b>	INTERNATIONAL APPLICATION NO. PCT/US99/26746	ATTORNEYS DOCKET NO P32185		
20. [X] The following fees are submitted:		CALCULATIONS PTO USE ONLY		
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):				
Search Report has been prepared by the EPO or JPO .....\$860.00		\$690.00		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) .....\$690.00				
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .....\$710.00				
Neither International Preliminary Examination Fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$1,000.00				
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$100.00				
ENTER APPROPRIATE BASIC FEE AMOUNT =		\$690.00		
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$0.00		
Claims	Number Filed	Number Extra	Rate	
Total claims	<b>31 - 20 =</b>	<b>11</b>	<b>11 x \$18.00</b>	<b>\$198.00</b>
Independent claims	<b>4 - 3 =</b>	<b>1</b>	<b>1 x \$80.00</b>	<b>\$80.00</b>
Multiple dependent claims (if applicable)		+ \$270.00		\$270.00
TOTAL OF ABOVE CALCULATIONS =				<b>\$1238.00</b>
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$
SUBTOTAL =				<b>\$1238.00</b>
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				\$
TOTAL NATIONAL FEE =				<b>\$1238.00</b>
		Amount to be refunded	\$	
		charged	\$	

- a.  A check in the amount of \$\_\_\_\_\_ to cover the above fees is enclosed.
- b.  Please charge my Deposit Account No. 19-2570 in the amount of **\$1238.00** to cover the above fees.  
A duplicate copy of this sheet is enclosed.
- c.  The Commissioner is hereby authorized to charge any additional fees which may be required, or  
credit any overpayment to Deposit Account No. 19-2570. A duplicate copy of this sheet is enclosed.
- d.  General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for  
extension of time relating to this application (37 CFR 1.136 (a)(3)).

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to  
revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

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#3

**"EXPRESS MAIL CERTIFICATE"**  
"EXPRESS MAIL" MAILING LABEL NUMBER EL737870035US  
**DATE OF DEPOSIT 11 JULY 2001**

Attorney Docket No. P32185

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INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE
CLAIMED		
PCT/US99/26746	12 November 1999	12 November 1998

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**TITLE OF INVENTION**  
**NOVEL METHOD OF TREATMENT**

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**APPLICANT(S) FOR DO/US**  
Lisa BENINCOSA and William JUSKO

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**PRELIMINARY AMENDMENT**

Preliminary to the examination of this application, Applicants respectfully request amendment of the above-identified application as follows:

**In the Claims:**

Please amend claim 17.

17. (Amended) A pharmaceutical composition according to claim 16 wherein the composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration over a sustained period of time.

**REMARKS**

Applicants have amended the dependency of claim 17. No new matter has been introduced.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

  
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Int'l App. No.: PCT/US99/26746  
Int'l Filing Date: 12 November 1999

**"VERSION WITH MARKING TO SHOW CHANGES MADE"**

**In the Claims:**

17. (Amended) A pharmaceutical composition according to claim [17] 16 wherein the composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration over a sustained period of time.

09/831652

JC18 Rec'd PCT/PTO 11 MAY 2001

**"EXPRESS MAIL CERTIFICATE"**  
"EXPRESS MAIL" MAILING LABEL NUMBER EL231307627US  
DATE OF DEPOSIT 11 MAY 2001

Attorney Docket No. P32185

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**TITLE OF INVENTION**  
**NOVEL METHOD OF TREATMENT**

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**APPLICANT(S) FOR DO/US**  
Lisa BENINCOSA and William JUSKO

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**PRELIMINARY AMENDMENT**

Preliminary to the examination of this application, Applicants respectfully request amendment of the above-identified application as follows:

**In the Specification:**

Kindly add the Abstract enclosed herewith on a separate sheet, at the end.

**In the Claims:**

Please amend claims 3-6, 8, 10, 15 and 19-20.

3. (Amended) A method according to claim 2, wherein the Threshold Plasma Concentration is within the range of from about 50 to about 120ng/mL or about 60 to about 120ng/mL or about 90 to about 110ng/mL or about 95 to about 105ng/mL.

4. (Amended) A method according to claim 1, wherein a minimum value of the Threshold Plasma Concentration (or the Minimum Threshold Plasma Concentration) of the insulin sensitiser is its SC50 concentration.

5. (Amended) A method according to claim 4, wherein a Preferred Threshold Plasma Concentration for the insulin sensitiser is twice the SC50 concentration.

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6. (Amended) A method according to claim 1, wherein the plasma concentration of the insulin sensitiser remains substantially within the range from the Minimum Threshold Plasma Concentration to a level at or above the Preferred Threshold Plasma Concentration.
8. (Amended) A method according to claim 7, wherein the insulin sensitiser is Compound (I) and the SC50 is within the range of 40 to 65 ng/mL.
10. (Amended) A method according to claim 7, wherein the insulin sensitiser is Compound (I) and the Preferred Threshold Plasma Concentration is in the range of about 80 to about 130 ng/mL or about 82.2 to about 123.4ng/mL.
15. (Amended) A method according to any one of claims 1 to 6, wherein the insulin sensitiser is selected from the group consisting of: 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) and 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone).
19. (Amended) A modified release composition according to claim 18 being a delayed, pulsed or sustained release composition.
20. (Amended) A composition according to claim 16, adapted to provide a method of treatment according to claim 1.

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**REMARKS**

The above-identified application is being entered into the National Phase from PCT application no. PCT/US99/26746.

Applicants have amended the claims to put them in conformity with U.S. practice.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

No new matter has been introduced.

Respectfully submitted,



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**"VERSION WITH MARKING TO SHOW CHANGES MADE"**

**In the specification:**

An abstract has been added.

**In the claims:**

3. (Amended) A method according to [claim 1 or] claim 2, wherein the Threshold Plasma Concentration is within the range of from about 50 to about 120ng/mL or about 60 to about 120ng/mL or about 90 to about 110ng/mL or about 95 to about 105ng/mL.

4. (Amended) A method according to [any one of] claim[s] 1 [to 3], wherein a minimum value of the Threshold Plasma Concentration (or the Minimum Threshold Plasma Concentration) of the insulin sensitiser is its SC50 concentration.

5. (Amended) A method according to [any one of] claim [1 to] 4, wherein a Preferred Threshold Plasma Concentration for the insulin sensitiser is twice the SC50 concentration.

6. (Amended) A method according to [any one of] claim 1 [to 5], wherein the plasma concentration of the insulin sensitiser remains substantially within the range from the Minimum Threshold Plasma Concentration to a level at or above the Preferred Threshold Plasma Concentration.

8. (Amended) A method according to [any one of] claim[s 4 to 6] 7, wherein the insulin sensitiser is Compound (I) and the SC50 is within the range of 40 to 65 ng/mL.

10. (Amended) A method according to [any one of] claim[s 6 to 9] 7 wherein the insulin sensitiser is Compound (I) and the Preferred Threshold Plasma Concentration is in the range of about 80 to about 130 ng/mL or about 82.2 to about 123.4ng/mL.

15. (Amended) A method according to any one of claims 1 to 6, wherein the insulin sensitiser is

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selected from the group consisting of 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) [or] and 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone).

19. (Amended) A modified release composition according to claim [1] 18 being a delayed, pulsed or sustained release composition.

20. (Amended) A composition according to [ny one of] claim 16 [to 19], adapted to provide a method of treatment according to [any one] of claim[s] 1 [to 15].

100 90 80 70 60 50 40 30 20 10

NOVEL METHOD OF TREATMENT

## FIELD OF THE INVENTION

5 This invention relates to a novel method of treatment, in particular to a method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus and a pharmaceutical composition for use in such a method.

## BACKGROUND OF THE INVENTION

10 European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter "Compound (I)"). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 15 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as "insulin sensitiser". In particular Compound (I) is a thiazolidinedione insulin sensitiser.

European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 20 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione insulin sensitiser.

Another series of compounds generally recognised as having insulin sensitiser 25 activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as "cyclic insulin sensitiser". Other examples of acyclic insulin sensitiser are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

30 Examples of other insulin sensitiser are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

The above mentioned publications are incorporated herein by reference.

It is now surprisingly indicated that the particular plasma concentrations of an anti-35 diabetic agent, such as Compound (I), which provide effective glycaemic control, indeed an

optimum effect on glycaemic control, can be determined. This therefore enables optimization of the dosing regimen for the anti-diabetic agent for a given dosing interval. Pharmaceutical compositions which provide plasma concentrations of an anti-diabetic agent, such as Compound (I), at these particular concentrations, especially over an extended 5 period of time, are also envisaged by this invention.

## SUMMARY OF THE INVENTION

Accordingly, in a first aspect, the present invention provides a method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus, 10 which method comprises the administration to a human or non-human mammal in need thereof, of an effective non-toxic amount of an insulin sensitiser, such as Compound (I), so as to provide a plasma concentration of the insulin sensitiser of at least a threshold level from within the range of effective plasma levels of the insulin sensitiser (hereinafter referred to as the "Threshold Plasma Concentration").

15

## DETAILED DESCRIPTION OF THE INVENTION

The Threshold Plasma Concentration is suitably within the range of from 40 to 200ng/nL including 50 to 200ng/nL, including 50 to 120ng/mL, 60 to 120ng/mL, 90 to 110ng/mL or 95 to 105ng/mL.

20 A suitable minimum Threshold Plasma Concentration (hereinafter "Minimum Threshold Plasma Concentration") is the SC50 concentration of the particular insulin sensitiser, which for Compound (I) is within the range of 40 to 65 ng/mL, more suitably 41.1 to 61.7, for example 50 or, more suitably, 51.4ng/mL.

25 A preferred Threshold Plasma Concentration (hereinafter "Preferred Threshold Plasma Concentration") is twice the SC50 concentration, which for Compound (I) is in the range of 80 to 130 ng/mL, more suitably 82.2 to 123.4, for example 100 ng/mL or 102.8 ng/mL.

30 The invention particularly envisages treatments wherein the plasma concentration of the insulin sensitiser remains substantially within the range of concentrations from the Minimum Threshold Plasma Concentration to the Preferred Threshold Plasma Concentration, that is for Compound (I) within the range of from 40 to 130 ng/mL, more suitably 41.1ng/mL to 123.4 ng/mL, for example 50ng/mL to 100ng/mL or 51.4ng/mL to 102.8 ng/mL.

35 The invention also particularly envisages treatments wherein the plasma concentration of the insulin sensitiser remains substantially within the range of

concentrations from the Minimum Threshold Plasma Concentration to a level at or above the Preferred Threshold Plasma Concentration, that is for Compound (I) within the range of from 40ng/mL to a level at or above 130 ng/mL, more suitably 41.1ng/mL to a level at or above 123.4 ng/mL, for example 50ng/mL to 100ng/mL or 51.4 ng/mL to a level at or above 5 102.8 ng/mL.

In its preferred form, the invention provides a treatment wherein the plasma concentration of the insulin sensitiser remains substantially at or above the Preferred Threshold Plasma Concentration, that is for Compound (I), substantially at or above 100ng/mL, especially substantially at or above 102.8ng/mL.

10 A suitable thiazolidinedione insulin sensitiser is Compound (I).

Other suitable thiazolidinedione insulin sensitisers include 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone).

A particular thiazolidinedione insulin sensitiser is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

20 A particular thiazolidinedione insulin sensitiser is 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone).

When the insulin sensitiser is Compound (I), the unit dose suitably comprises 2 to 12 or preferably 4 to 8 mg of Compound (I) in a pharmaceutically acceptable form.

25 Suitable unit dosages of other insulin sensitisers are those indicated in publications mentioned herein and include from 100 to 800mg of troglitazone such as 200, 400, 600 or 800mg and for pioglitazone from 5 to 50mg, including 10 to 40mg, such as 20, 30 or 40 mg and also including 15, 30 and 45mg of pioglitazone

30 As indicated above, the treatment of the invention is suitably effected by the administration of a pharmaceutical composition of the insulin sensitiser adapted so as to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser.

Accordingly, in a further aspect, the invention also provides a pharmaceutical composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier therefor, which composition is adapted to provide a plasma concentration of the insulin

sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser, suitably over a sustained period of time.

Suitable modified release compositions are delayed, pulsed or sustained release compositions.

5        Accordingly, in a further aspect, the invention also provides a modified release pharmaceutical composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier therefor, which composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser, suitably over a sustained period of time.

10      Suitably the carrier is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration.

Suitably the modified release is a sustained release, for example providing effective release of active agents of at least a Threshold Plasma Concentration over a time period of up to 24 hours.

15      Suitably the modified release is a pulsed release, for example providing two pulses of release of active agents of at least a Threshold Plasma Concentration per 24 hours.

The invention particularly envisages compositions adapted to provide a plasma concentration of the insulin sensitiser which remains substantially within the range of concentrations from the Minimum Threshold Plasma Concentration to the Preferred 20 Threshold Plasma Concentration, that is for Compound (I) within the range of from 40 to 130 ng/mL, more suitably 41.1 to 123.4 ng/mL, for example 50 to 100ng/mL or 51.4 to 102.8 ng/mL.

The invention also envisages compositions adapted to provide a plasma concentration of the insulin sensitiser which remains substantially at or above the Preferred 25 Threshold Plasma Concentration, that is for Compound (I), substantially at or above 100ng/mL, especially substantially at or above 102.8ng/mL.

Suitably the composition is a unit dose composition.

Suitably, the Threshold Plasma concentration of the insulin sensitiser is maintained or exceeded over several hours, for example 12, 16 or 24 hours, per dose of insulin 30 sensitiser.

Suitably, the treatment is such that the Threshold Plasma concentration of the insulin sensitiser is maintained or exceeded over a sustained period of time.

It will be understood that the insulin sensitiser, such as Compound (I), is administered in a pharmaceutically acceptable form, including pharmaceutically acceptable 35 derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as

appropriate of the relevant pharmaceutically active agent. It will be understood that all pharmaceutically acceptable forms of the active agents *per se* are encompassed by this invention.

5 Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in EP 0306228 and WO94/05659. A preferred pharmaceutically acceptable salt is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

10 Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

15 Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures thereof. Compound (I) contains a chiral carbon atom, and hence can exist in up to two stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

20 The insulin sensitisers mentioned herein are prepared in accordance with known methods, for example those disclosed in the above mentioned publications or in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press).

25 When used herein the term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

30 "Conditions associated with diabetes mellitus itself" include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

"Complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy.

Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinary acceptable compound.

When used herein the term "SC50 concentration" refers to the plasma concentration for a given compound required to produce a half-maximal effect on fasting plasma glucose for that compound.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts, of Compound (I) in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of Compound (I) *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which contains 2 mg of Compound (I).

Diabetes mellitus is preferably Type II diabetes.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using standard methodology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390 and Frank P., "Monitoring the Diabetic Patient with Glycosolated Hemoglobin Measurements", Clinical Products 1988.

Preferably, the treatment of the invention will effect an improvement in the levels of advanced glycosylation end products (AGEs), leptin and serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof, in particular an improvement in serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof.

As indicated above, the active medicaments of the method of the invention are preferably administered in pharmaceutical composition form.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of 5 the invention is in the form of a unit dose.

Unit dosage presentation forms for oral administration may be in tablet or capsule form and may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrants and wetting agents.

Examples of binding agents include acacia, alginic acid, carboxymethylcellulose 10 calcium, carboxymethylcellulose sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, tragacanth.

15 Examples of fillers include calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, 20 maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, xylitol.

25 Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, zinc stearate.

Examples of glidants include colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, talc.

30 Examples of disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrilin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycollate.

An example of a pharmaceutically acceptable wetting agent is sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, 10 hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if 15 desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or 20 ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agent can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the 25 Compound (I) suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

As indicated the compositions are preferably in a unit dosage form in an amount appropriate for the relevant daily dosage.

30 The present treatments and compositions may also contain other medicaments in addition to insulin sensitizers including other anti diabetic agents, such as insulin secretagogues, biguanide antihyperglycaemic agents and alpha glucosidase inhibitor antihyperglycaemic agents.

In the treatment the medicaments may be administered from 1 to 6 times a day, 35 suitably 1 or 2 times per day, preferably once per day.

Compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

5 The method by which the Threshold Plasma Concentration, such as the SC50 concentration, for a given compound can be determined is:

1) first to obtain plasma concentrations versus time data for the compound, preferably using data from humans, by using standard pharmacokinetic compartmental modelling methods (for example for Compound (I), concentrations were fit to a one compartment model.);

10 2) the model predicted concentrations for the compound are then fed back into the model and used to determine the change in fasting plasma glucose levels after various doses;

15 3) the relationship between predicted plasma concentrations of compound and fasting plasma glucose can suitably be determined using an indirect pharmacological response model (model IV), for example that described in (Dayneka NL, Garg V and Jusko WJ, Comparison of Four Basic Models of Indirect Pharmacodynamic Responses. *J of Pharmacokinetics and Biopharmaceutics*. Vol 21, No 4. 1993). This model yields estimates of glucose input rate (Kin) and output rate (Kout), maximal stimulation of glucose output (Smax). Hill coefficient (gamma) and the Threshold Plasma Concentration, such as the

20 SC50 concentration (i.e the concentration associated with a half maximal response) to be determined for that compound. This method forms a further part of the present invention.

For Compound (I), it was necessary to account for a time delay between the time of actual initiation of dosing (week 0) and the observed change in fasting plasma glucose. This delay factor was estimated through the modelling for each dose level. The mean delay 25 across dose levels for Compound (I) was found to be 292 hours. The delay factor was incorporated into the model for deriving fasting plasma glucose by assuming that the first dose of drug occurred only after the time dictated by the delay factor. It is considered that for this model a delay factor would be required for other thiazolidinedione insulin sensitizers and that this factor will be substantially similar to that found for Compound (I). Delay 30 factors for other compounds may also be required to be determined using similar methodology to that disclosed herein.

The invention also comprises the above mentioned method, optionally including the step of introducing the delay factor into the model.

In a further aspect, the invention provides a process for preparing a pharmaceutical 35 composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier

therefor, the composition being adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser, which process comprises formulating the insulin sensitiser and the pharmaceutically acceptable carrier so as to provide a plasma concentration of the insulin sensitiser of at least a

5 Threshold Plasma Concentration of the insulin sensitiser.

Suitably, the composition is a modified release composition.

Suitably, the carrier is adapted so as to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration.

The compositions for the treatment are prepared and formulated according to

10 conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books) or the above mentioned publications.

15 The modified release compositions may be formulated according to appropriate methods disclosed in for example Sustained and Controlled Release Drug Delivery Systems, Editor Joe R Robinson, Volume 7, published by Marcel Dekker under the title Drugs and the Pharmaceutical Sciences, Controlled Drug Delivery, 2nd Edition' edited by Joe Robinson and Vince Lee, Marcel Dekker, 1987 and 'Drug Delivery to the Gastrointestinal Tract' Editors: J G Hardy, S S. Davis and C G Wilson also with reference to texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

20

25 No adverse toxicological effects are expected for the compositions or methods of the invention in the above mentioned dosage ranges.

## EXAMPLES

**Example: Pharmacokinetic/Pharmacodynamic Modeling of Compound (I) in Type 2 Diabetes Patients**

30 A PK/PD model was developed to characterise the effect of Compound (I) on fasting plasma glucose (FPG) concentrations in diabetic patients. The model was developed using mean fasting plasma glucose data from a Phase III clinical trial which consisted of comparison of placebo and four doses/regimens of Compound (I) in a parallel-group design

of 26 weeks duration. Dose regimens evaluated were: 4 mg once daily and 2 mg twice daily, and 8 mg once daily and 4 mg twice daily.

#### Pharmacokinetics of Compound (I)

5 The pharmacokinetics of Compound (I) were described using a one-compartment model with first order oral absorption. Individual bayesian estimates of Compound (I) oral clearance and steady-state volume of distribution were predicted for each patient in the same Phase III clinical trial utilizing the population parameter estimates (priors) from the Phase I population pharmacokinetic analysis. Mean concentration-time profiles (C<sub>p</sub>) for each 10 regimen for use in the pharmacodynamic modeling were predicted using the mean post hoc oral clearance (2.68 L/h) and V<sub>ss</sub>/F (15.4 L) values across these patients (Figure 1).

#### Pharmacodynamics of Compound (I)

15 A modified indirect response model IV (Dayneka et al. 1993) was developed utilizing the pharmacokinetics of Compound (I) as the driving force for the change in fasting plasma glucose after various doses of Compound (I). Modeling fittings were done using ADAPT II, Release 4 (D'Argenio and Schumitzky, 1979).

20 In the absence of Compound (I), plasma glucose levels are governed by formation (kin) and utilization (kout). The action of Compound (I) was described as stimulation (S(t)) of the utilization of plasma glucose (kout), described in text as FPG reduction (Eq. 1). S<sub>max</sub> represents the maximal stimulation, SC<sub>50</sub> is the Compound (I) concentration associated with half-maximal stimulation and γ represents a sigmoidicity parameter in the Hill type function (Eq. 2).

25

$$\frac{dFPG}{dt} = k_{in} - k_{out} \cdot S(t) \cdot FPG \quad \text{Eq 1.}$$

where

$$S(t) = \frac{S_{max} \cdot C_P^\gamma}{SC_{50}^\gamma + C_P^\gamma} \quad \text{Eq 2.}$$

30 The mean fasting plasma glucose profiles from 6 weeks prior to dosing (time 0) through 26 weeks of treatment for the 5 treatment groups are shown in Figure 2. The PK/PD model accommodates the full nature of the fasting plasma glucose response over the duration of the study period as evidenced by the close agreement between observed and predicted fasting plasma glucose concentrations (Figure 2). An estimated lag-time (292

hours) between the first dose and onset of response was incorporated into the modeling. The lag-time allows the model to describe the slow onset of action of Compound (I) observed over the first 4 weeks of dosing.

5 The fitted plasma glucose concentrations at steady-state reflect the difference in response to varying total daily dose as well as different dosing frequencies (i.e. once vs twice daily) (Figure 2). The estimated pharmacodynamic parameter values are shown in the table below:

Parameter	Estimate	CV %
$k_{in}$ , mg/dL of FPG per h	0.54	4.5
$k_{out}$ , h <sup>-1</sup>	0.0023	4.5
$S_{max}$	0.44	7.1
$SC_{50}$	51.4	10.7
$\gamma$	3.1	36.6

10 Based on these data, the  $S_{max}$  of the model suggests a maximum FPG reduction of 160 mg/dL.

15 Although clinically meaningful reductions in glycaemia are evident with once daily dosing of Compound (I), the observation from study 024 that twice daily dosing tended to be more efficacious than once daily can be explained by differences in the concentration-time profiles of Compound (I) across these dosage regimens. Following twice daily dosing of 4 mg, Compound (I) concentrations remain above the  $SC_{50}$  for approximately 21 hours compared with only 14 hours following once daily dosing with 8 mg (Figure 1).

20 **Conclusion**

The differential effects on FPG reduction following once vs twice daily dosing are well described with a PK/PD model.

**References**

25 D'Argenio, DZ and Schumitzky, A (1979). A Program Package for Simulation and Parameter Estimation in Pharmacokinetics. *Computer Programs in Biomedicine*. 9:115-1134.

Dayneka NL, Garg V and Jusko WJ (1993). Comparison of Four Basic Models of Indirect Pharmacodynamic Responses. *Journal of Pharmacokinetics and Biopharmaceutics*. Vol 21 (No. 4): 457-478.

5        The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein  
10 by reference as though fully set forth.

What is claimed is:

1. A method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus, which method comprises the administration to a human or non-human mammal in need thereof, of an effective non-toxic amount of an insulin sensitiser so as to provide a plasma concentration of the insulin sensitiser of at least a threshold level (the Threshold Plasma Concentration) from within the range of effective plasma levels of the insulin sensitiser.
- 10 2. A method according to claim 1, wherein the Threshold Plasma Concentration is within the range of from about 40 to about 200ng/nL.
- 15 3. A method according to claim 1 or claim 2, wherein the Threshold Plasma Concentration is within the range of from about 50 to about 120ng/mL or about 60 to about 120ng/mL or about 90 to about 110ng/mL or about 95 to about 105ng/mL.
- 20 4. A method according to any one of claims 1 to 3, wherein a minimum value of the Threshold Plasma Concentration (or the Minimum Threshold Plasma Concentration) of the insulin sensitiser is its SC50 concentration.
- 25 5. A method according to any one of claim 1 to 4, wherein a Preferred Threshold Plasma Concentration for the insulin sensitiser is twice the SC50 concentration.
- 30 6. A method according to any one of claim 1 to 5, wherein the plasma concentration of the insulin sensitiser remains substantially within the range from the Minimum Threshold Plasma Concentration to a level at or above the Preferred Threshold Plasma Concentration.
7. A method according to any one of claim 1 to 6, wherein the insulin sensitiser is Compound (I).
- 35 8. A method according to any one of claims 4 to 6, wherein the insulin sensitiser is Compound (I) and the SC50 is within the range of 40 to 65 ng/mL.

9. A method according to claim 8, wherein the SC50 of Compound (I) is 51.4ng/mL.

10. A method according to any one of claims 6 to 9 wherein the insulin sensitiser is Compound (I) and the Preferred Threshold Plasma Concentration is in the range of about 80 to about 130 ng/mL or about 82.2 to about 123.4.

11. A method according to claim 10, wherein the Preferred Threshold Plasma Concentration for Compound (I) is 100 ng/mL or 102.8 ng/mL.

10 12. A method according to claim 1, wherein the insulin sensitiser is Compound (I) and its plasma concentration remains substantially within the range of from 40 ng/mL to at or above 130 ng/mL or 41.1 ng/mL to at or above 123.4 ng/mL, for example 50ng/mL to at or above 100ng/mL or 51.4ng/mL to at or above 102.8ng/mL.

15 13. A method according to claim 10, wherein the insulin sensitiser is Compound (I) and its plasma concentration remains substantially at or above its Preferred Threshold Plasma Concentration.

20 14. A method according to claim 13, wherein the insulin sensitiser is Compound (I) and its plasma concentration remains at or above 100ng/mL or substantially at or above 102.8ng/mL.

25 15. A method according to any one of claims 1 to 6, wherein the insulin sensitiser is 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone).

30 16. A pharmaceutical composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier therefor, which composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser.

17. A pharmaceutical composition according to claim 17 wherein the composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration over a sustained period of time.

5 18. A modified release pharmaceutical composition comprising an insulin sensitiser and a pharmaceutically acceptable carrier therefor, which composition is adapted to provide a plasma concentration of the insulin sensitiser of at least a Threshold Plasma Concentration of the insulin sensitiser.

10 19. A modified release composition according to claim 1 being a delayed, pulsed or sustained release composition.

20. A composition according to any one of claim 16 to 19, adapted to provide a method of treatment according to any one of claims 1 to 15.

15 21. A method by which the Threshold Plasma Concentration for a given anti diabetic compound can be determined by the steps:

20 1) first to obtain plasma concentrations versus time data for the compound by using standard pharmacokinetic compartmental modelling methods;

2) the model predicted concentrations for the compound are then fed back into the model and used to determine the change in fasting plasma glucose levels after various doses;

25 3) the relationship between predicted plasma concentrations of compound and fasting plasma glucose can then be determined using an indirect pharmacological response model.

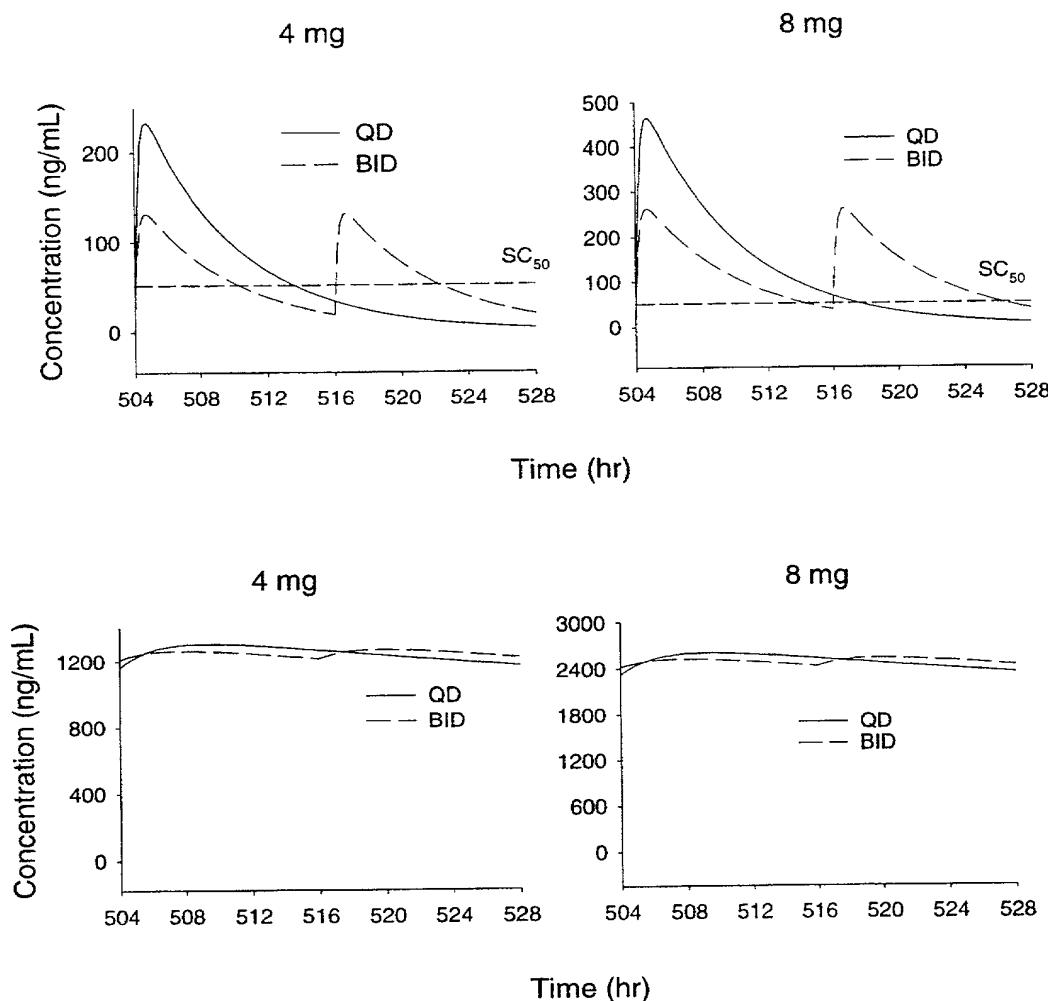
**ABSTRACT OF THE DISCLOSURE**

A method for the treatment of Type 2 diabetes mellitus and conditions associated with diabetes mellitus, which method comprises the administration to a human or non-human mammal in need thereof, of an effective non-toxic amount of an insulin sensitiser so as to provide a plasma concentration of the insulin sensitiser of at least a threshold level (the 'Threshold Plasma Concentration') from within the range of effective plasma levels of the insulin sensitiser, compositions for use in such method and methodology for determining plasma concentrations of active agent use in such methods.

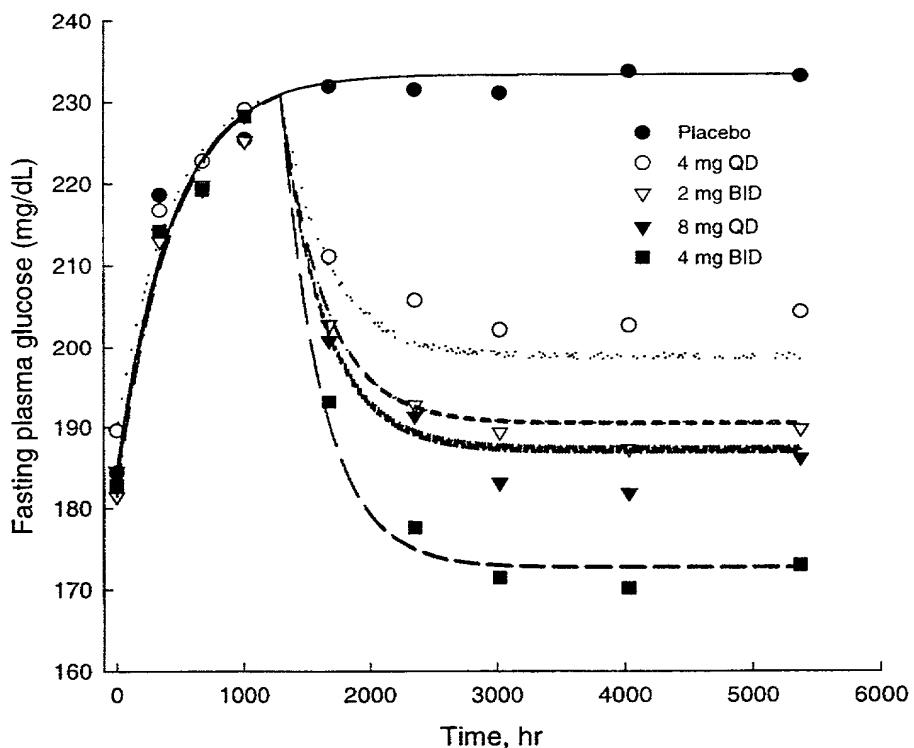
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**Figure 1: Simulated steady-state concentrations of Compound (I) (upper) and M10 (lower) over a 24 hour dosing interval following 4 mg and 8 mg total daily doses of Avandia**



**Figure 2: Observed mean fasting glucose concentrations and predicted mean fasting plasma glucose concentrations vs time based on PK/PD modeling of the effect of Compound (I) concentrations by regimen following administration of Avandia**



Symbols represent observed FPG, lines represent predicted FPG.

Time scale related to study definition: 0 hr = -6 week

1008 hr = 0 week (initiation of first dose)

1680 hr = 4 week

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

## NOVEL METHOD OF TREATMENT

the specification of which (check one)

[ ] is attached hereto.

[ X ] was filed on 12 November 1999 as Serial No. PCT/US99/26746  
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

## Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9824893.3	GB	12 November 1998	Yes No

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
--------------------	-------------

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status
------------	-------------	--------

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

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Serial No.	Filing Date	Status
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I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Lisa BENINCOSA

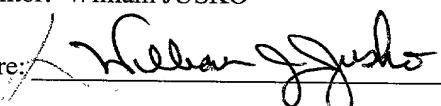
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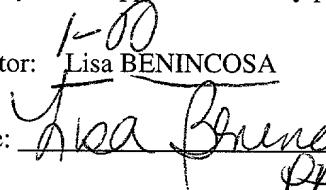
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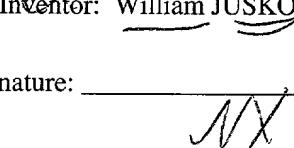
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